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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,840	06/28/2001	Catherine Guenther	R-409	4993

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	15

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/895,840	GUENTHER, CATHERINE	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,48 and 50-96* is/are pending in the application.

4a) Of the above claim(s) *16 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 16, 48 and 50-96 are pending in the application. Claims 16 and 48 are withdrawn from consideration for being directed to non-elected subject matter.

This Office Action is in response to the Amendment filed on 5/13/03.

Response to Amendment

The objection to claim 2 is moot in light of Applicant's cancellation of the claims.

The rejection of claims 5-15, 17-47 and 49 under 35 U.S.C.112 1st paragraph is moot in light of Applicant's cancellation of the claims.

The rejection of claims 1-4, 9, 10, 17-39, 41, 42 and 46 under 35 U.S.C.112 2nd paragraph is moot in light of Applicant's cancellation of the claims.

The rejection of claims 1-8 and 10 under 35 U.S.C.103 (a) is moot in light of Applicant's cancellation of the claims.

Newly added claims 50-96 are rejected under 35 U.S.C.112 1st paragraph for reasons set forth of the record mailed on 9/9/02 and further discussed below.

Newly added claims 54-56, 57, 59-87 and 90-96 are rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Newly added claims 50-58 are rejected under 35 U.S.C.103 (a) for reasons set forth of the record mailed on 9/9/03 and further discussed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-61 and 90-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are rejected for same reasons as applied to claims 11-15 and 44-47, which are discussed in detail in the previous office action (paper no.13, see page 2-3). Briefly, the claims are drawn to a method of identifying an agent that modulates the RORγ gene expression and function by administering an agent to a RORγ gene knockout mouse, or cells derived from said mouse, and determine whether the expression or function of RORγ gene is modulated. The claims are further drawn to a method of identifying agents that ameliorate a phenotype of the RORγ gene disruption by determining the expression of the RORγ gene in a RORγ gene knockout mouse. However, the specification does not teach a specific method in determining the expression or function of RORγ in a RORγ knockout mouse. It is not known how to determine the expression or function of a gene that has already been knocked out. Therefore, one skilled in the art would have to engage in undue experimentation to practice the method as claimed. If this aspect of rejection can be overcome, the scope of enablement rejection set forth below is applicable.

Claims 50-58, 62-89, 95 and 96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic knockout mouse comprising a homozygous disruption in the RORγ gene, wherein no RORγ is produced, and said mouse exhibits phenotypic features such as increased spleen weight, thymic cortical expansion,

medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to the wild type mouse, and a method of producing said transgenic mouse by homologous recombination in mouse ES cells, does not reasonably provide enablement for transgenic and/or knockout mice without any phenotype. Further, the specification is not enabling for a transgenic mouse or cell isolated from said mouse comprising any kind of disruption in RORγ gene. Moreover, the specification is not enabling for a method of producing said mouse by homologous recombination in any type of cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are rejected for same reasons as applied to claims 5-10, 17-43 and 49, which are discussed in detail in the previous office action (paper no.13, see page 4-9). The specification is only enabling for a transgenic knockout mouse comprising a homozygous disruption in the RORγ gene, wherein no RORγ is produced, and said mouse exhibits phenotypic features such as increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to the wild type mouse, and a method of producing said transgenic mouse by homologous recombination in mouse ES cells. As discussed in the previous office action, the phenotype of the transgenic mouse is unpredictable. In addition, the specification teaches a heterozygous transgenic mouse having ROR disruption does not exhibit any phenotype as the homozygous transgenic mouse. The specification does not teach how to use a transgenic mouse without any phenotype. Therefore, the phenotype of the mouse is the essential element for the enablement of the claims (must be

recited in the claims) because one of ordinary skill of art would not know how to use transgenic mouse without any phenotype.

The specification does not provide an enabling disclosure for a transgenic knockout mouse comprising any type of disruption of the RORγ gene. The specification teaches that "disruption" encompasses insertion, deletion, frameshift, replacement of a promoter, enhancer which results in partial or complete inhibition of production of the RORγ protein, or enhancement of the RORγ activity. However, the specification only teaches a transgenic mouse comprising homologous knockout of the RORγ gene, which results in complete inhibition of the gene expression. The specification teaches such transgenic knockout mice exhibit the phenotype such as increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma. For reasons discussed in the previous office action, the state of art recognize that the phenotype of the transgenic mouse cannot be accurately predicted. As such, whether other types of disruption would result in the same phenotype is unpredictable. Therefore, the specification is not enabling for a transgenic knockout mouse comprising any type of disruption of the RORγ gene.

As discussed in the previous office action, since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The specification does not teach a method of making transgenic knockout mice by homologous recombination in other types of cell. Therefore, the claimed method of making a transgenic mouse is not enabled for gene targeting in any type of cell except mouse ES cell.

The specification teaches, according to Table 1, only the female knockout mouse but not the male knockout mouse exhibits a slight increase in liver and kidney weight. As such, the specification only enables the female homozygous knockout mouse for phenotypic feature such as increased liver, kidney weight, and increased liver, kidney to body ratio. Similarly, according to Table 1, there is no significant difference in thymus weight between knockout or wild type mouse. Therefore, the specification is not enabled for transgenic mouse having increased thymus weight and thymus body ration.

In summary, the specification only enables a transgenic knockout mouse comprising a homozygous disruption in the RORγ gene, wherein no RORγ is produced, and said mouse exhibits phenotypic features such as increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to the wild type mouse, and a method of producing said transgenic mouse by homologous recombination in mouse ES cells. For reasons discussed in the previous office action and above, the specification does not provide support for the enablement of the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-56, 57, 59-87 and 90-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 54-56, 57, 59-87, 90-92 and 96, the recitation of "a target sequence disrupted by homologous recombination of the target gene sequence with a sequence

homologous to a region of SEQ ID NO:1" renders the claims indefinite because it is unclear how the target sequence is disrupted. In other words, it is unclear what type of mutation is introduced to the target sequence because homologous recombination with a region of the target sequence by itself does not disrupt the gene.

Claims 69-71 recite the limitation "liver abnormality" in line 1. There is insufficient antecedent basis for this limitation in the claim. The parent claim, claim 62, does not recite this limitation.

Regarding claims 79 and 80, the term "abnormality lymphocytes" renders the claims indefinite. It should be "abnormality in lymphocytes" as recited in the parent claim.

Claims 93 and 94 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to determine a phenotype such as a spleen abnormality is ameliorated by an agent if said agent modulates poor grooming. The nexus between modulation of the recited symptoms of disease and ameliorate the recited phenotype appears to be missing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 50-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Medvedev et al. (Genomics 1997, Vol 46, pages 93-102, AG).

The teachings of the references and the reasons for obviousness of the claimed invention in view of the prior art were discussed in detail in the previous office action. Applicant argues that neither reference by itself teaches the generation of a knockout RORγ mouse. Applicant is reminded one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Examiner recognize that the obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Medvedev et al. teach the importance in studying RORγ because its possible implication in a variety of malignancies including lymphomas and renal carcinomas. Mansour et al. teach that transgenic knockout mouse model is an important approach to study gene function (see page 349, 1st paragraph, lines 10-11). In addition, Mansour et al. provides a model which can be used to produce a homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Medvedev et al. provide the cloned RORγ sequence, which is identical to SEQ ID NO:1 (see Figure 1). In view of combined

teaching of Medvedev et al and Mansour et al., it would have been obvious to one of ordinary skill of art to make a RORγ target construct, introducing said construct to mouse ES cells and generate a RORγ knockout mouse to study the function of the RORγ gene. Therefore, the invention would have been prima facie obvious to one of ordinary skill of art at the time the invention was filed.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
August 8, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER